REMARKS

Prior to entry of the present amendment, claims 63-65, 67, 70-78, and 84-92 were pending. Claims 63-65, 67, 70-78, and 84-92 are rejected under 35 U.S.C. § 112, first paragraph. Applicants address each basis for rejection as follows.

Claim Amendments

Claims 63, 72, 73, 75, and 76 have been amended to replace "comprising" language with "consisting of" language. In addition, claim 63 has been amended to require the proteinaceous recognition domain to be conformationally constrained by covalent bonding *at both its extremities* to a platform. Support for this amendment is found, for example, in the second full paragraph at page 13 of the specification as filed.

New claims 93-101 have been added. Recitation, in claims 93-101, of a eukaryotic cell, for instance, a mammalian or yeast cell, finds support, for example, in the third full paragraph at page 29 of the specification as filed. Claims 96 and 99 also find support, for example, at the top of page 15, in the paragraph bridging pages 36 and 37, and in the first full paragraph at page 37 of the specification as filed.

Claims 85-92 have been cancelled.

No new matter has been added by the present amendments. Applicants reserve the right to pursue any cancelled subject matter in this or in a continuation or divisional application.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 63-65, 67, 70-78, and 84-92 stand rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of written description and enablement in the specification as filed. Claims 85-92 have been cancelled and rejection of these claims, therefore, is moot. As applied to the pending claims, Applicants, for the following reasons, respectfully disagree with the written description and enablement rejections.

Written Description

The Office states (page 3):

> [T]he claims are directed to a recognition molecule that can vary in length, hence may not function as desired, knowing that structural changes can affect the structure-function relationship of a protein. No correlation is made between structure and function.
>
> * * *
>
> Therefore, the skilled artisan cannot envision the detailed chemical structure of the peptide aptamer and TRX [thioredoxin]-like protein encompassed in the claims.

Applicants respectfully submit that the present claims are free of this basis for rejection.

As an initial matter, Applicants note that claim 63 has been amended to require the intracellular recognition molecule to *consist of* a proteinaceous recognition domain covalently bonded at both its extremities to a platform. The proteinaceous recognition domain is further required to be a peptide aptamer of five to sixty amino acids. Hence, while the peptide aptamer recited in the claim can vary in length, it cannot be shorter than five amino acids or longer than sixty amino acids. Applicants submit that the specification as filed adequately describes such peptide aptamer containing recognition molecules.

The specification, for example, at the top of page 3, states that the present invention stems from the finding that, for any given target molecule, a peptide aptamer recognition molecule that interacts with the target with a K_d of less than 1×10^{-9} may be designed. The specification as filed describes various peptide aptamers that are encompassed by the claims. For instance, in Example 1, the specification describes anti-Cdk2 aptamers and in Example 4, the specification describes anti-Bax aptamers. Moreover, for example, at the bottom of page 59, to the top of page 62, the specification describes methods that can be used to generate and modify aptamers. One skilled in the art would recognize that these techniques are applicable to any number of proteins. As such, Applicants submit that the description in the specification of aptamers is not limited

to the particular recited examples, but rather provides adequate description of peptide aptamers within the full scope of the claims.

In addition, claim 63 as amended requires the proteinaceous recognition domain to be conformationally constrained by covalent bonding at both its extremities to a platform. Conformationally constraining the proteinaceous recognition domain in this manner provides a structural limitation which, as taught throughout the specification, reduces the flexibility of the recognition domain and, therefore, correlates with its function as an aptamer interacting with a target molecule with the required affinity.

With regard to the platform, Applicants note that claim 63 requires the platform to be thioredoxin or a thioredoxin-like protein. The structure of thioredoxin from various species was known at the time of filing (as described, for example, at the top of page 15 of the specification). In addition, the structure of thioredoxin-like proteins having a three-dimensional structure substantially similar to that of thioredoxin (e.g., glutaredoxin) was also known at the time of filing (see, e.g., the top of page 15). As such, the specification describes that thioredoxin and thioredoxin-like proteins can be used to conformationally constrain the intracellular recognition molecule. Applicants maintain that one skilled in the art would recognize that the exact sequence of the platform is not critical so long as it can function to conformationally constrain the intracellular recognition molecule. In fact, the specification, at page 14, in the second full paragraph, states that the platform "can be any molecule which is capable of reducing, through covalent bonding, the number of conformations which [the intracellular recognition molecule] can assume" and provides numerous examples of conformation constraining proteins and peptides including thioredoxin and thioredoxin-like proteins.

Further, in the March 3, 2006 reply, Applicants submitted evidence in support of the term "thioredoxin-like protein" being well known in this art, and those skilled in the art therefore recognizing what "thioredoxin-like proteins" are. Given the knowledge in the art of thioredoxin, thioredoxin-like proteins, and their structure, Applicants submit

that one skilled in the art would recognize that Applicants were in possession of the genus of thioredoxin-like proteins. The claims should not be limited to particular thioredoxin-like proteins. For all the above reasons, Applicants submit that the recognition domain and the thioredoxin or thioredoxin-like platform recited in claim 63 is adequately described in the specification as filed. These bases for the written description rejection should be withdrawn.

The Office also asserts, at page 4, that recitation of "comprising" language in claims 72, 73, 75, and 76 expands the length of the peptide beyond the 5 to 60 amino acids required by claim 63. Without agreeing with the Office, claims 72, 73, 75, and 76 have been amended to recite that the recognition domain *consists of* a mutant of a particular amino acid sequence where the mutant has from one to three amino acid changes with respect to the particular sequence. The particular sequences recited in these claims are 20 amino acids in length. As such, a change of one to three amino acids in these sequences clearly does not expand the length of the peptide beyond the length requirement of claim 63, from which claims 72, 73, 75, and 76 depend. This basis for the written description rejection may be withdrawn.

Turning to new claims 96-101, Applicants note that these claims require the peptide to include the sequence of SEQ ID NO:1, 2, 3, or 4 (claim 96) or to include a mutant of the amino acid sequence of SEQ ID NO:1, 2, 3, or 4, where the mutant consists of one to three amino acid changes with respect to the sequence of SEQ ID NO:1, 2, 3, or 4 (claim 99). Applicants' specification sets forth the sequences of SEQ ID NOS:1-4 and also, in the Examples, describes how these sequences can be mutated. There can be no doubt that one skilled in the art would recognize that, at the time of filing, Applicants were in possession of the particular sequences recited in claims 96 and 99 as well as sequences containing one to three amino acid changes in these particular sequences.

Moreover, claims 96 and 99 require the platform to be thioredoxin, human thioredoxin, or glutaredoxin. As noted above, the specification teaches that the sequence

and structure of thioredoxin and glutaredoxin were known in the art at the time of filing. Clearly, the platform proteins recited in new claims 96 and 99 are described in the application as filed.

Further, claims 96 and 99 require the cell to be a eukaryotic cell. Dependent claims require the eukaryotic cell either to be a mammalian cell (claims 97 and 100) or a yeast cell (claims 98 and 101). The specification, for example, in the third full paragraph at page 29 teaches that the interaction between the intracellular recognition molecule and the target molecule may occur in a eukaryotic cell, such as a mammalian or yeast cell. The specification, for instance, in Example 1 also provides experimental data resulting from interactions between exemplary intracellular recognition molecules and target molecules in yeast cells. Accordingly, the specification describes use, in eukaryotic cells, of the intracellular recognition molecules encompassed by the present claims. For all the above-reasons, Applicants submit that new claims 96-101 are free of the written description rejection.

Enablement

The Office states (pages 5 and 6):

> [T]he specification, while being enabling for intracellular recognition molecules that are peptide aptamers (such as the sequences disclosed on page 33 and anti-Cdk2 and others listed on page 12 of the specification as well as cited in the prior art), does not reasonably provide enablement for any intracellular recognition molecule or target or TRX-like protein.

As an initial matter, as indicated above, Applicants note that the independent claim, claim 63, requires the intracellular recognition molecule to be a peptide aptamer. As such, Applicants submit that the intracellular recognition molecules encompassed by the claims are ones which the Office has indicated to be enabled by Applicants' specification.

Claim 63 requires the proteinaceous recognition domain to consist of a peptide of five to sixty amino acids. Hence, the claims provide a defined length for the recognition domain. Moreover, the specification in Examples 1-5 describes methods that may be used to modify a recognition domain and to test its activity, and also describes examples of aptamers that have been modified and, after testing, have been found to bind their target with higher affinity (see, e.g., the anti-Cdk2 aptamers described in Example 1 and the anti-Bax aptamers described in Example 4). As such, the specification describes how one skilled in the art can make and use the peptide aptamers recited in the claims.

On this point, Applicants again direct the Office's attention to the Declaration of Dr. Pierre Colas filed on May 6, 2005 in which Dr. Colas states that, besides the anti-Cdk2 and anti-Bax aptamers described in the Examples, he successfully selected peptide aptamers against the GTPase activating protein RasGAP, the transcriptional repressor Fur, the adaptor protein Grb2, the protein kinases Raf, ERK1, and AKT1, and the chaperone Hsp70 using the two-hybrid system disclosed in the present application. Clearly the specification as filed enables the generation of peptide aptamer-containing recognition molecules against a wide variety of proteins. Given that the claims recite particular lengths for the peptide aptamer recognition domains and provide extensive teachings and examples as to how recognition molecules containing such aptamers may be modified and tested, Applicants submit that making and using the recognition molecules encompassed by the claims does not require undue experimentation. This basis of the enablement rejection may be withdrawn.

The thioredoxin-like molecules recited in claim 63 are also enabled by the specification as filed. The specification states (page 15):

> Thioredoxin-like proteins are defined herein as proteins having at least 18%, preferably at least 40% and more preferably at least 75% homology with the amino acid sequence of *E. coli* thioredoxin over an amino acid sequence length of 80 amino acids. Thioredoxin-like molecules also include peptides which have a three-dimensional structure substantially similar to that of human or *E. coli* thioredoxin, for example glutaredoxin.

(Citations omitted.)

Moreover, as noted above, in the March 3, 2006 reply, Applicants submitted evidence showing that the term "thioredoxin-like protein" is well known in this art, and therefore those skilled in the art would know what "thioredoxin-like proteins" are and could make and use them accordingly.

As noted above, the sequence and structure of thioredoxin was known at the time the application was filed. Similarly, the sequence and structure of glutaredoxin (a thioredoxin-like molecule) was known at the time of filing. Given these known sequences and structures and the teachings in Applicants' specification, Applicants submit that one skilled in the art could readily have obtained other thioredoxin-like sequences without undue experimentation using nothing more than techniques standard in the art of molecular biology. Further, the specification, for example, at the bottom of page 13, teaches how to conformationally constrain an aptamer in a platform (e.g., a thioredoxin-like protein) and, for example, at pages 62-63 describes how an interaction between an aptamer and its target may be assayed using a yeast two-hybrid system. As such, any inoperative thioredoxin-like molecules can readily be removed without undue experimentation.

For the reasons set forth above, Applicants submit that the intracellular recognition molecules encompassed by claim 63 and its dependent claims are fully enabled by the specification as filed. Moreover, with regard to new claims 96 and 99, Applicants submit that there can be no question that the specification enables one skilled in the art to make and use intracellular recognition molecules containing the particular sequences or mutants consisting of one to three changes in the particular sequences recited in the claim covalently bonded to thioredoxin, human thioredoxin, or glutaredoxin. Accordingly, Applicants submit that new claims 96-101 are also free of the enablement rejection.

Finally, the Office, at page 6, states that "the claims encompass a peptide aptamer (intracellular recognition molecule,) and any target bound to any TRX-like protein as a

platform interacting with an unspecified amount of targets." Applicants, as a matter of clarification, note that the peptide aptamer is covalently bonded to the platform, and it is this complex that interacts with the target. The target is not part of the peptide aptamer/platform complex (the intracellular recognition molecule), but rather interacts with the complex.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for three (3) months, to and including May 16, 2008, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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